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# Development of Rheumatoid Arthritis After Treatment of Large Granular Lymphocyte Leukemia With Deoxycoformycin

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**The association of T-cell large granular lymphocyte (LGL) leukemia and rheumatoid arthritis is well described and it is now recognized that these patients and patients with Felty's syndrome represent different aspects of a single disease process. Most patients have rheumatoid arthritis at the time of diagnosis of LGL leukemia. This is the first detailed report of the development of rheumatoid arthritis after the diagnosis and treatment of LGL leukemia as well as the first report of rheumatoid arthritis that occurred in association with deoxycoformycin treatment. It is likely that the beneficial sustained normalization of neutrophil counts as a result of deoxycoformycin treatment played a significant role in the development of this complication. Hematological improvement occurred despite molecular genetic evidence of persistence of the abnormal T-cell clone. The role of the clonally expanded T cells in the pathogenesis of neutropenia and rheumatoid arthritis is discussed. Am. J. Hematol. 57:253–257, 1998.** © 1998 Wiley-Liss, Inc.

**Key words: Felty's syndrome; autoimmunity; HLA-DR4; T-cell receptor; neutropenia**

## INTRODUCTION

The clinical syndrome of chronic neutropenia associated with increased numbers of circulating large granular lymphocytes (LGL) was first described in 1977 by McKenna et al. [1]. Subsequently, the term LGL leukemia was proposed, based on the observation of clonality and the demonstration of tissue invasion by these cells in bone marrow, spleen, and liver. This disease has been further classified into T-cell LGL leukemia and NK-cell LGL leukemia [2]. Rheumatoid arthritis has been associated with T-cell LGL leukemia but not the NK-cell variant. In Loughran's review, rheumatoid arthritis was noted in 28% of patients with T-LGL leukemia [3]. The temporal association of LGL leukemia to the onset of rheumatoid arthritis is variable. In previous reports [4–9], the majority of the patients had documented rheumatoid arthritis at the time of diagnosis of large granular lymphocytosis and a few patients presented with the simultaneous onset of both diseases. Loughran described one patient with clonal LGL proliferation, which preceded the development of rheumatoid arthritis by several years [3]. However, details of this case were not reported. Our report describes the development of rheumatoid arthritis after the diagnosis and treatment of T-cell LGL leukemia with deoxycoformycin. The development of rheumatoid arthritis after treatment with deoxycoformycin, an agent that produces T-cell depletion, has not been reported.



## CASE REPORT

A 48-year-old man with mild fatigue was found to have agranulocytosis and lymphocytosis in March 1993.

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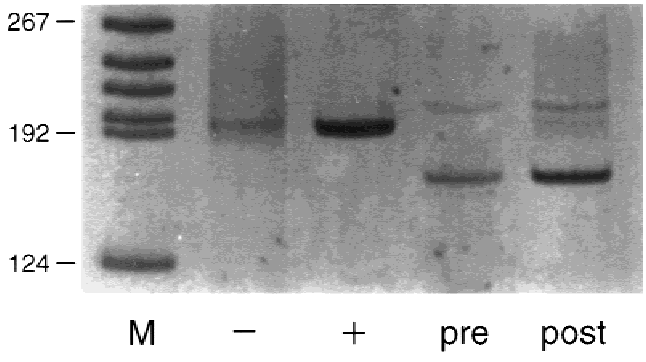


**Fig. 1. Polymerase chain reaction detection of clonal T-cell receptor gamma gene rearrangements. DNA was extracted from the viably frozen mononuclear cells using standard methodology, and PCR-amplified with a pair of consensus primers of the Variable and Joining regions of the TCR gamma gene, and analyzed on a 6% polyacrylamide gel. Both patient samples show apparently identically sized bands indicative of persistence of the clone. Southern blot analysis of the TCRβ locus (using Jβ1 and Jβ2 probes) confirmed the persistence of the clonal T-cell population after deoxycoformycin treatment. M, DNA molecular weight markers (pBR322 HaeIII) with representative sizes in base pairs, noted on the left; −, negative control DNA (extracted from tonsil); +, positive control DNA (Jurkat cell line); pre, bone marrow specimen from April 1993, before deoxycoformycin; post, peripheral blood specimen from November 1994, after deoxycoformycin.**

Physical examination was normal. Complete blood count showed a total white count of $18.5 \times 10^9$/L with 1% neutrophils, 10% atypical lymphocytes, and 76% lymphocytes. The hematocrit was 40.8% and the platelet count was $114 \times 10^9$/L. Peripheral blood smear showed large granular lymphocytes with low nuclear to cytoplasmic ratio and azurophilic granules. Flow cytometry showed that the majority of abnormal lymphocytes expressed CD2, CD3, CD5, CD7, CD8, CD16, and CD57. CT scans of the chest, abdomen, and pelvis showed splenomegaly (14 cm). The bone marrow was hypercellular with focal and interstitial lymphocytic infiltrates. A clonal T-cell expansion was also confirmed by polymerase chain reaction (PCR) method [10] using a set of primers specific for the variable [V] and joining [J] regions of the T-cell receptor gamma chain gene. A dominant band and a minor band were noted at approximately 140–150 and 190–200 bp, respectively (Fig. 1). HLA typing was positive for class I antigens A2, A11, B50, B70, Cw06, Cw07, and class II antigens DRB1*04, DRB1*15, DRB4*01, DRB5*0101, DQB1*03, DQB1*06. In early April 1993, the patient was admitted to the hospital for febrile neutropenia and treated with intravenous antibiotics and G-CSF. He received G-CSF 300 mcg/day for 9 days and attained a total white blood cell count of $39.3 \times 10^9$/L with 29% neutrophils and 7% bands. The patient was referred to the National Cancer Institute for further management. He had another episode of neutropenic fever, necessitating hospital admission and treatment with broad spectrum antibiotics and G-CSF. He received G-CSF 300 mcg/day for 6 days and attained a total white blood cell counts of $40 \times 10^9$/L with 50% neutrophils. During that time, he noted a mild degree of bone and joint pain, which was attributed to G-CSF. Evaluation was negative for neutrophil antibodies, hepatitis B surface antigen, and HIV serology. Serum immunoglobulin levels were normal. Rheumatoid factor level was slightly elevated at 1:32 and ANA was negative.

The patient was enrolled on a phase II trial of deoxycoformycin for treatment of LGL leukemia in May 1993. Deoxycoformycin, 4 mg/m$^2$ by slow intravenous injection weekly, was administered with G-CSF ($3 \times 300$ μg after the first dose and $1 \times 300$ μg after the second dose of deoxycoformycin) because of the previous episodes of febrile neutropenia. Apart from a mild degree of bone and joint pain, he tolerated treatment well. After the third deoxycoformycin dose (without G-CSF), the patient noticed swelling and pain of his metacarpophalangeal joint and proximal interphalangeal joints bilaterally. Bilateral shoulder, elbow, wrist, and knee pain was reported but no inflammation was noted. Radiographic examination of the joints showed soft tissue swelling without bony erosion. Rheumatoid factor level had increased to 1:320 and the sedimentation rate was 35 mm. At this time, minimal hematologic improvement was noted and the granulocyte count remained below 500/μL. He was diagnosed with early rheumatoid arthritis and was treated with trilisate 1,000 mg po tid, prednisone 10 mg po qd, and plaquenil 200 mg po bid. With this regimen, the patient's arthritis improved and deoxycoformycin was continued for three more doses without G-CSF support. The neutrophil count normalized although peripheral blood and bone marrow studies showed persistent T-cell LGL leukemia. PCR analysis confirmed that the clonal proliferation of lymphocytes was unaffected by treatment with deoxycoformycin. The patient has maintained normal neutrophil counts for almost 4 years and has had no significant infectious complications since completing treatment. The most recent complete blood count of April 1997 showed a total white blood cell count of $6.05 \times 10^9$/L with 47% neutrophils, 39% lymphocytes (60–70% large granular lymphocytes), 10% monocytes, 3% eosinophils, and 1% basophils. The hematocrit was 44.6% and platelet count $187 \times 10^9$/L. His rheumatoid arthritis remained clinically active with an elevated erythrocyte sedimentation rate, synovitis, joint effusions, and the development of rheumatoid nodules for more than 1 year after completing therapy. He gradually improved and prednisone was stopped in November 1995, but plaquenil and trilisate were continued.

## DISCUSSION

This case report raises interesting questions about the association of LGL leukemia and rheumatoid arthritis. About one third of the patients with T-cell LGL leukemia have rheumatoid arthritis but the temporal sequence of these events is variable. This report illustrates that diagnosis of LGL leukemia can precede diagnosis of rheumatoid arthritis, although it is likely that simultaneous diagnosis would have occurred if the patient had higher granulocyte counts at presentation. Since most cases of LGL leukemia are recognized during investigation of clinically significant neutropenia, there might be a delay in the diagnosis of LGL leukemia. Since occasionally, clonal expansion of lymphocytes with a characteristic CD3+, CD57+ phenotype may occur without LGL morphology in the peripheral smear [11,12], workup should not be restricted to a morphologic examination of the peripheral blood. Rather, immunophenotypic and clonality studies should be performed when rheumatoid arthritis is diagnosed. By thorough investigation, a better understanding of the temporal relationship between LGL leukemia and rheumatoid arthritis will emerge. Loughran [3] observed one patient who had a clonal LGL proliferation for several years prior to the development of rheumatoid arthritis. Studies performed after the diagnosis of rheumatoid arthritis showed a normal lymphocyte phenotype and disappearance of the abnormal clone by Southern blot hybridization analysis. He raises the possibility that rheumatoid arthritis may be preceded by a clonal lymphoproliferation that is no longer apparent at diagnosis of rheumatoid arthritis. This was not the case in our patient; a clone of cells with a monoclonally rearranged T-cell receptor gamma chain gene (possibly biallelic) was present before the development of rheumatoid arthritis and persisted after treatment was completed.

A second question is what precipitated the development of rheumatoid arthritis. It is of interest that our patient developed rheumatoid arthritis following treatment with deoxycoformycin. This purine analog produces severe depletion of both CD4+ and CD8+ T-cell subsets [13] and it is paradoxical that rheumatoid arthritis should occur in this setting. In another patient, with rheumatoid arthritis and hairy cell leukemia, treated at our institution with deoxycoformycin, joint pain and inflammation improved for many years following treatment but returned at the time of disease relapse. The role of neutrophils and the administration of G-CSF in the development of rheumatoid arthritis in this patient may be important. The patient received G-CSF during two neutropenic febrile episodes without evidence of arthritis and following the first two doses of deoxycoformycin. Flare up or reactivation of rheumatoid arthritis during or after treatment with G-CSF or GM-CSF for neutropenia in Felty's syndrome and rheumatoid arthritis has been reported [14–19]. In these reports, increased joint inflammation was seen in patients with a preexisting diagnosis of rheumatoid arthritis and the signs of disease activity promptly abated upon G- or GM-CSF withdrawal. In contrast, our patient had no preceding diagnosis of rheumatoid arthritis, no objective signs of joint inflammation during two prolonged courses of G-CSF with markedly elevated granulocyte counts, and had active rheumatoid arthritis for more than 1 year after completing therapy. It seems likely that deoxycoformycin permitted expression of rheumatoid arthritis by restoring normal granulocyte counts. Exacerbation of rheumatoid arthritis has been reported in association with improvement of granulocytopenia in a patient with Felty's syndrome following splenectomy [15].

HLA typing showed the patient to be positive for HLA DRB1*04 (HLADR4). The association of HLA-DR4 with susceptibility to rheumatoid arthritis has been reported [20,21]. HLA-DR4 was found in over 90% of the patients with Felty's syndrome [22,23] and it is now recognized that patients with LGL leukemia and rheumatoid arthritis and patients with Felty's syndrome represent a single disease process characterized by rheumatoid arthritis, neutropenia, LGL expansion, HLA-DR4 expression, and splenomegaly [24,25]. Patients with LGL leukemia and rheumatoid arthritis have the HLA DRB1*04 genotype common in Felty's syndrome whereas patients with LGL leukemia without rheumatoid arthritis have a similar level of DRB1*04 expression as the control population. Oligoclonal T cells that express Vβ-3, -14, and -17 are found in synovial fluid of patients with rheumatoid arthritis [26,27]. Persistent oligoclonal expansion of peripheral blood Vβ-3 but not Vβ-14 or -17 CD8+ T cells has also been observed in patients with rheumatoid arthritis [28], but a similar pattern of expression was not seen in peripheral blood samples of patients with LGL leukemia and rheumatoid arthritis. In a series of seven patients with LGL leukemia and rheumatoid arthritis, three had rearrangement of Vβ-6 genes although no unique patterns of junctional sequence rearrangements were seen for patients with both diseases [29]. It will be important, however, to correlate HLA haplotypes with the pattern of T-cell gene rearrangement to obtain a better understanding of the relationship between LGL leukemia and rheumatoid arthritis. It remains possible that a common antigenic stimulus initiates both disorders and this could be best explained by knowing whether a particular HLA allele is associated with a specific TCR gene rearrangement. This would best be determined in a population homozygous for HLA haplotypes with increased risk of rheumatoid arthritis. The risk ratios for patients with HLA haplotypes Dw4(DRB1*0401), Dw14(DRB1*0404), and Dw1(DRB1*0101) are increased whereas HLA-DR1/DR5, DR2, DR2/DR3, and DR3/DR7 are protective [30].

Further investigation and analysis of these observations should be considered to improve knowledge of the pathogenesis of rheumatoid arthritis and LGL leukemia.

Neutropenia resolved in this patient despite persistence of the abnormal T-cell clone. Several possibilities can be considered. A change in cytokine expression or FAS ligand expression in the T-LGL cells may account for his hematological improvement. CD34+ hematopoietic precursors express FAS (CD95) in response to interferon gamma, tumor necrosis factor, or the combination [31,32] and undergo apoptosis in response to interaction with FAS ligand, a cell surface molecule expressed and shed by LGL leukemia cells [33]. Deoxycoformycin may have affected cytokine expression by LGL cells thereby protecting CD34+ precursors from apoptosis. Alternatively, FAS ligand expression may have been altered on the T-LGL cells. A third possibility is an alteration in the TCR αβ recognition sequence that may be responsible for the clinical changes that occurred in this patient after treatment with deoxycoformycin. A TCR αβ sequence that recognized neutrophils may have been altered so that neutrophils were no longer targeted for destruction and a new recognition site may have facilitated development of rheumatoid arthritis in this patient.

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